

Review: inhaled long acting β_2 agonists are effective and safe in stable chronic asthma

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Walters EH, Walters JA, Gibson MD. Inhaled long acting beta agonists for stable chronic asthma. *Cochrane Database Syst Rev* 2003(4):CD001385.

Clinical impact ratings GP/FP/Primary care ★★★★★☆☆ Internal medicine ★★★★★☆☆ Allergy ★★★★★☆☆ Respiriology ★★★★★☆☆

Q In people with stable chronic asthma, are inhaled long acting β_2 agonists (LABAs) effective and safe?

METHODS



Data sources: Cochrane Airways Review Group's randomised controlled trial (RCT) register (includes studies from searches of Medline, EMBASE/Excerpta Medica, and CINAHL); hand searches of 20 high yield respiratory care journals; reference lists; and contact with researchers.



Study selection and assessment: RCTs that compared inhaled LABAs (salmeterol or formoterol), given twice daily, with placebo in adults or children who have had asthma for ≥ 3 months. Studies that included people with other pulmonary diseases (particularly smoking related chronic obstructive pulmonary disease) were excluded.



Outcomes: daytime and night-time asthma symptom scores, daily peak flow measurement, bronchodilator use for symptom relief, asthma exacerbation rates, and adverse effects.

MAIN RESULTS

85 RCTs (94 comparisons; 56 parallel, 29 crossover) met the selection criteria. 71 RCTs included adults or adolescents >12 years of age, and 14 included children <12 years of age. LABAs reduced symptoms in the morning (18 RCTs, standardised mean difference [SMD] -0.32 , 95% CI -0.40 to -0.25) and evening (11 RCTs, SMD -0.43 , CI -0.59 to -0.26). LABAs also increased peak expiratory flow (PEF) in the morning (19 RCTs, weighted mean difference [WMD] 26.8 l/min, 95% CI 20.4 to 33.2) and evening (13 RCTs, WMD 19.2 l/min, CI 11.6 to 26.7). FEV₁ was greater after treatment with LABAs than with placebo (17 RCTs, WMD 0.18 l, CI 0.13 to 0.23). Participants in the LABA group used rescue bronchodilators less often during a 24 hour period than those in the placebo group (12 RCTs, change from baseline WMD -1.2 puffs, CI -1.6 to -0.87) and had fewer major exacerbations (table). The difference in forced vital capacity was not

statistically significant (2 RCTs). LABAs led to more headache than placebo (14 RCTs) (table).

CONCLUSION

In people with stable chronic asthma, inhaled long acting β_2 agonists were effective and safe.

Commentary

After a single inhalation, the bronchodilating effects of LABAs last ≥ 12 hours. However, their safety has been debated in the scientific literature for >10 years.

The systematic review by Walters *et al* used a comprehensive search strategy and rigorous review methods. They concluded that LABAs improve symptoms, spirometry, and asthma exacerbations when compared with no LABAs. Subgroup analysis showed greater benefit in patients already on inhaled corticosteroids. However, pooled data in children (5 RCTs) suggested an increased risk of exacerbation with LABAs. Their regular use was associated with a bronchoprotective effect of 1.5 to 1.8 doubling doses of methacholine.

The review overlooks several important issues. Firstly, heterogeneity in airway inflammation was not considered. LABAs do not have clear anti-inflammatory effects and can mask a smouldering eosinophilic inflammation,¹ particularly when the inhaled corticosteroid dose is also reduced. Well conducted RCTs have shown that LABA monotherapy can worsen asthma.^{2,3} Thus, the clinical relevance of a comparison with placebo becomes doubtful. Secondly, studies have not compared full and partial agonists. Development of tolerance to the bronchoprotective effect may be more likely with a full agonist than with a partial agonist, particularly in patients who are homozygous for arginine in codon 16 of the β_2 receptor gene.⁴ Indeed, a recent analysis found that the adverse effects of salmeterol monotherapy were greater in this set of patients (presented at the 2004 National Heart Lung Blood Institute Workshop on Clinical Research in Asthma).

In summary, although this meta-analysis shows a benefit for LABAs relative to placebo, insufficient evidence exists to recommend monotherapy with LABAs. They can be considered as add on therapy for patients who are symptomatic on moderate doses of inhaled corticosteroids or even after airway eosinophilic inflammation is controlled. The role of genetic polymorphism of the β_2 receptor in predicting adverse outcomes and the role in children need further evaluation.

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- McIvor RA, Pizzichini E, Turner MO, *et al*. Potential masking effects of salmeterol on airway inflammation in asthma. *Am J Respir Crit Care Med* 1998;158:924–30.
- Lemanske RF Jr, Sorkness CA, Mauger EA, *et al*. Inhaled corticosteroid reduction and elimination in patients with persistent asthma receiving salmeterol: a randomized controlled trial. *JAMA* 2001;285:2594–603.
- Lazarus SC, Boushey HA, Fahy JV, *et al*. Long-acting beta2-agonist monotherapy vs continued therapy with inhaled corticosteroids in patients with persistent asthma: a randomized controlled trial. *JAMA* 2001;285:2583–93.
- Lee DK, Currie GP, Hall IP, *et al*. The arginine-16 beta2-adrenoceptor polymorphism predisposes to bronchoprotective subsensitivity in patients treated with formoterol and salmeterol. *Br J Clin Pharmacol* 2004;57:68–75.

Inhaled long acting β_2 agonists v placebo for stable chronic asthma*

Outcomes at 2–52 weeks	Weighted event rates			NNT (CI)
	β_2 agonists	Placebo	RRR (95% CI)	
Major exacerbation	19%	23%	16% (9 to 23)	25 (20 to 50)
			RRI (CI)	NNH (CI)
Headache	5.6%	4.6%	29% (1 to 66)	100 (33 to ∞)

*Abbreviations defined in glossary; weighted event rates, RRR, RRI, NNT, NNH, and CI calculated from data in article.

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